Return to NINDS Parkinson's Disease Research Web

Non-motor Research

Principal Investigator: ASHE, JAMES
Grant Number: 2R01NS040106-05
Title: Learning in the human motor cortex

Abstract: The long-term objective of this proposal is to understand how the brain learns and control movement sequences. As Lashley recognized more than half a century ago, much of our behavior, from the performance of organized movements to the ability to use language, is based on our capacity to detect, learn, and produce sequences. In the current proposal, we use variants of the serial reaction time (SRT) task and functional imaging in human subjects to examine the neural substrates responsible for learning the fundamental structure of movement sequences, the brain areas responsible for modulating learning through reward and punishment, and the extent to which the brain uses similar strategies for learning temporal and spatial sequences. We will test the following hypotheses. (1) During sequence learning cortical motor areas detect and learn transitions from one element to the next, while the basal ganglia encode the whole structure of sequenced movements. (2) Reward and punishment have direct but differential effects on motor sequence learning and this will be reflected by proportional changes in the activity of the basal ganglia. (3) Learning sequences of temporal intervals will engage a similar set of brain areas to those involved in learning spatial sequences and will not involve the cerebellum. Impairment in the ability to produce sequences is an important component of the disability experienced by patients with Parkinson's disease. The work outlined here will provide a fundamental understanding of these disabilities and may lead to the development of strategies for rehabilitation and treatment of these patients.-

Principal Investigator: Biglan, Kevin M
Grant Number: 2L30NS050062-02
Title: Clinically Meaningful Outcomes in Parkinson's Disease

Abstract: Unavailable

Principal Investigator: BOYLAN, LAURA S
Grant Number: 1L30NS049909-01
Title: Emotion/Depression in Epilepsy & Parkinson's Disease

Abstract: Unavailable

Principal Investigator: CHEN, HONGLEI
Grant Number: 1K08NS048468-01
Title: Diet, gene-diet interactions and risk of Parkinson's

Abstract: The candidate, Honglei Chen, M.D., Ph.D., has more than two years research experience in Parkinson's disease (PD) and is currently a Research Associate at Harvard School of Public Health. Dr. Chen's research interest includes the environmental and genetic etiology of sporadic PD and that of other neurodegenerative diseases, and he plans to develop an independent academic career in this area. In this K08 proposal, Dr. Chen proposes a large prospective investigation of diet and risk of sporadic PD in the Cancer Prevention Study-ll Nutrition Cohort (CPS-IIn) and a large nested case-control study of PD with genetic polymorphisms and gene-diet interactions in the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS). In the CPS-IIn, he will prospectively examine among 162,408 US men and women associations of PD with dietary intakes, focusing on folate, coffee, dietary antioxidants, fat, alcohol, and dairy products. Confirmation of incident PD cases in CPS-IIn is ongoing and they expect to document 550 definite and probable PD cases diagnosed between 1992 and 2001. In the HPFS and NHS cohorts, he will evaluate the associations of PD risk with common polymorphisms of NAT2, CYP1A2, ADH2, ADH3, ADH4, and MTHFR. He also will, for the first time, explore gene-diet interactions in PD etiology, including NAT2, CYP1A2 and caffeine intake; ADH2, ADH3, ADH4, and alcohol intake; and MTHFR and folate intake. Through the year of 2000, they have documented 567 definite and probable PD cases and 454 of them provided either blood or cheek cells for genetic analysis. In this proposed nested case-control study, two controls will be selected for each PD case matching on age and gender. All three cohorts included in this proposal are well-established large prospective cohorts with comprehensive (baseline and updated) and validated dietary assessments and rigorous outcome ascertainments. Moreover, the scope of this study makes it one of the largest investigations to date. The completed or nearly completed data collection will further make this study most cost-effective. Therefore, this K08 grant will simultaneously accomplish two important goals: helping Dr. Chen develop the skills to become an independent researcher in the epidemiology of neurological diseases and furthering our understanding of the complex interrelationships among diet, genes and PD etiology. -

Principal Investigator: DICKSON, DENNIS W
Grant Number: 2P50NS040256-06
Title: Genetics and Molecular Biology of Parkinsonism

Abstract: The Udall Center for Excellence in Parkinson's Disease Research at the Mayo Clinic is an integrated, multidisciplinary center that studies the Genetics and Molecular Biology of Parkinsonism. The Center draws upon the clinical strengths of the Mayo Clinic Movement Disorder Section as well as epidemiologic and longitudinal studies of Parkinson's disease (PD), dementia with Lewy bodies and aging that provide clinical material for research projects. The Clinical Core is a multi-national effort to identify and characterize multiplex families with PD for genetic studies of PD. The Clinical Core also recruits and follows sporadic PD patients and arranges for postmortem studies. The Genetic Core provides genetic screening and performs genome wide linkage studies of familial PD. When permission is granted, samples are submitted to the NINDS DNA repository. The Neuropathology Core performs postmortem evaluations of PD, provides histologic support for projects and provides postmortem material collected through several different avenues for the research projects. Project 1 builds upon progress from the previous funding period demonstrating multiplication of the alpha-synuclein gene (SCNA) in autosomal dominant, early-onset PD and focuses on population genetics of SNCA, characterization of SNCA multiplications (including the size and genes within the multiplication regions), and measuring temporal and regional alpha-synuclein expression in normals and a-synucleinopathies. Project 2 is a clinicopathologic study that determines the frequency and clinical expression of Lewy bodies in normal individuals using the Mayo Medical Records Linkage System, with studies on the role of neuronal loss, inflammation and tau on clinical features. Project 3 uses cell lines that inducibly express alpha-synuclein as well as mitochondrial toxins, such as rotenone, to study truncated and aggregated alpha-synuclein with the goal of determining the role of interacting proteins in aggregate formation and the effects of aggregates on proteasome function and gene expression.-

Principal Investigator: FARLEY, BECKY G
Grant Number: 5R21NS043711-02
Title: Think big, from voice to limb movement rehabilitation

Abstract: We will test the efficacy of an innovative treatment technique that could induce a radical paradigm shift in movement rehabilitation for people with Parkinson disease (PD). Based upon an extremely successful speech treatment for people with idiopathic PD (the Lee Silverman Voice Treatment (LSVT(R)), people with PD will undergo intensive practice of high effort/large amplitude arm movements and learn to transfer their "big effort" to everyday movements. Unlike other physical therapy approaches with unclear efficacy, the LSVT(R) approach has clearly demonstrated both short and long term efficacy up to two years. In addition, LSVT(R) is supported by hypotheses put forth to explain hypokinesia and bradykinesia in people with PD, therefore, it is easily applied to limb movements. Fifty subjects will be randomly assigned to one of two interventions with similar intensity regimens, think big therapy (novel) or traditional physical therapy (control). Speech studies have shown that a treatment with a simple focus (think loud) may generalize to affect motor output in other systems (e.g., articulation, speaking rate, swallowing, respiratory mechanics). Thus, we predict that learning to perform bigger arm movements will also improve arm speed, based upon the well described relationship between movement speed and amplitude. In addition, we will document the generalizability of this technique to improve arm and leg function. Although both groups may show improvements given the intense work schedule, we predict that improvements in the think big therapy will be greater than in the traditional physical therapy (control) group. Measurements will include physiological tests for assessing arm movement speed and amplitude using kinematic techniques. As "sense of effort" is the primary proposed mechanism underlying this treatment approach, we will measure sense of effort. Additional measurements will include tests of arm and leg function (strength, timed ADL tasks, gait, handwriting), a standardized clinical assessment (UPDRS), and a subjective rating scale. If successful, we plan to 1) further validate retention of treatment effects and generalizability of this technique (speech to limb; limb to speech) and 2) develop a standardized protocol that can be used for training physical therapists.-

Principal Investigator: FELLOWS, LESLEY K
Grant Number: 5R21NS045074-02
Title: Mapping the Anatomy of Decision Making

Abstract: Decision-making, the process of choosing between options, is a fundamental human behavior. Despite its ubiquity and importance, little is known about the neural substrates of this cognitive process. Impaired decision-making is an important symptom of a variety of neurological and psychiatric disorders, ranging from frontotemporal dementia to drug addiction. Focal injury to the ventral part of the frontal lobes, such as follows aneurysm rupture or closed head injury, seems to lead to selective impairment in decision making. This proposal describes work designed to break new ground in the cognitive neuroscience of decision-making. A series of exploratory studies based on classical decision-making theory will identify the neural substrates of this fundamental aspect of human cognition. The specific goals of this work are to (a) develop novel tasks that operationalize the core cognitive processes of human decision making by adapting experimental paradigms from psychology and economics, (b) use these tasks to identify the neural substrates of these fundamental elements of decision making: at the neuroanatomical level by evaluating patients with fixed lesions of the frontal lobes, and at the neurochemical level by studying patients with Parkinson's disease, (c) determine how impairments in basic reinforcement processing and learning in these patient populations may contribute to poor decision making both on the gambling task and in life, and (d) apply these decision making tasks to better characterize the frontal dysfunction of patients with frontotemporal dementia. Innovative behavioral methods adapted from decision-making research across multiple disciplines will be employed to study decision making in patients with fixed lesions of ventral or dorsal prefrontal cortex, Parkinson's disease, or normal subjects administered drugs that manipulate relevant neurochemical systems. This work will serve the long-term aim of establishing a framework to study the component processes of decision-making in the human brain, in both health and disease. This approach has the potential to provide insights into the basis for a wide range of pathological human behavior.-

Principal Investigator: FREY, KIRK A
Grant Number: 5P01NS015655-24
Title: PET Study of Biochemistry and Metabolism of the CNS

Abstract: This Program Project focuses on in vivo neurochemistry of human neurological disorders, emphasizing subcortical structures and their interactions in neurodegenerative and idiopathic functional disorders of movement. Studies in the proposal combine neurochemical phenotypes with functional measures, the latter including motor performance, blood flow activation, neurotransmitter release, ans aspects of sleep physiology. The Program consists of 4 Scientific Projects and 3 Cores. Project by Kilbourn, "New Radiotracers for Neurological PET", will introduce a novel functional approach to assessment of GABAA receptors through allosteric ligands of the chloride ionophore. GABAergic projects are critical components of striatal output and other extrapyrimidal sites. Assessment of GABAA function will complement glucose metabolism studies that may preferentially reflect excitatory glutamatergic pathways. Project by Frey, "Striatal Dopamine and Motor Performance in Aging and Parkinson's Disease" will determine functional motor correlates of nigrostriatal dopaminergic losses in aging and Parkinson's disease and will assess their reversal by acute dopaminergic challenge. Project by Gilman, "Neurochemical and Sleep Disorders in Multiple System Atrophy", will assess the relationships between disrupted sleep in extrapyrimidal neurodegeneration and brain stem cholinergic projections. Project by Albin, "Dopamine Synaptic Mechanisms in Tourette Syndrome", will assess striatal dopaminergic projects and their function from a multi-faceted approach, including measures of their density, their capacity for dopamine re-uptake, their capacity for dopamine release, and an assessment of ambient synaptic dopamine occupancy of D2-type dopamine receptors. Cyclotron/Radiochemistry, Tomography and Data Analysis, and Administrative Core functions support each Project. Overall , the disorders under study in this Program are of unknown pathogenesis and have only symptomatic therapies. The proposed studies will lead to enhanced insight into extrapyrimidal neurochemistry and will address important aspects of dysfunction and disability in these disorders. Novel and improved therapies and new pathophysiological mechanisms and insight may ultimately result. -

Principal Investigator: GROSSMAN, MURRAY
Grant Number: 5R01NS035867-07
Title: Cognitive Impairments in Parkinson's Disease and Aging

Abstract: We seek converging evidence from cognitive studies of non-demented patients with Parkinson's disease (PD), electrocortical event-related potentials (CEPs), and functional magnetic resonance imaging (fMRI) to test our interactive neurocognitive model of core cognitive processes and executive resources in comprehension. Specific Aim 1 manipulates executive resources (working memory, strategic planning, inhibitory control) in ambiguous sentences. PD patients' impaired sentence comprehension will be related to limitations in specific executive resources. Resource-related slowing of CEPs will be seen in PD for the same material. fMRI in young subjects with this material will recruit interactive neural networks for sentence processing: left ventral inferior frontal cortex (vIFC) and left posterolateral temporal cortex (PLTC) for core language processes, and specific cognitive resources in left dorsal IFC (dIFC), prefrontal cortex, striatum, and right PLTC. To compensate for age- and disease-related resource limitations, healthy seniors and PD patients will up-regulate resource-related networks, but we expect no change in the core sentence processing network. Specific Aim 2 tests a material-neutral deficit for rules that depends on implicit memory. We examine regular and irregular morphology in verbs and nouns, and assess non-linguistic concept acquisition mediated by implicit- or rule-based learning. PD patients will show a material-specific deficit for rules in verbs. fMRI in young subjects will recruit left vIFC only for regular verb morphology, and dIFC for decision-making resources. d]FC will be up-regulated in aging and PD. Specific Aim 3 assesses the generalizeability of our model to prosody comprehension. PD patients judge acoustically simple and complex prosody stimuli at baseline and during a secondary task. Restricted resources will limit PD patients' comprehension of complex prosody. fMRI in young subjects will recruit orbital frontal and dIFC only for complex prosody, and dIFC will be up-regulated in aging and PD. Our data support a componential neurocognitive architecture consisting of dynamically interactive networks modified to process sentences depending on available resources and relative demand. -

Principal Investigator: HOLROYD, SUZANNE
Grant Number: 5R01NS045008-02
Title: Parkinsons disease:Visual dysfunction and hallucinations

Abstract: The purpose of this three year grant is to examine the relationship between visual hallucinations and visual system abnormality in Parkinson's disease. Visual hallucinations are common symptoms and frequent causes of morbidity in Parkinson's disease, yet little is known about their etiology. Increasing evidence suggests that hallucinations in Parkinson's disease are not simply a medication effect, but are associated with the underlying disease process. Specificallly, evidence exists that suggest visual hallucinations in Parkinson's disease may be related to known visual system dysfunction in Parkinson's disease. In this study, thirty Parkinson's disease patients with visual hallucinations will be matched to thirty Parkinson's disease patients without visual hallucinations. They will be examined on neuropsychological tests assessing visual cognitive function, and will undergo visual evoked potentials. A subset of these patients (20 matched pairs) will also undergo functional magnetic resonance imaging (fMRI) to assess visual cortex function. It is hypothesized that Parkinson's disease patients with visual hallucinations will have greater evidence of visual system abnormality. Specifically they will demonstrate greater deficits of visual-cognitive function, greater latency on visual evoked potential and differences in activation of visual cortical regions on functional magnetic resonance imaging (fMRI) than those without visual hallucinations. It is hypothesized that these results will support a proposed biologic model of VH in PD regarding the role of dopamine abnormality in both the retina and basal ganglia that effect the regulation of function of visual cortex. The results of this study will increase knowledge regarding the neural mechanisms of visual hallucinations in Parkinson's disease and knowledge of visual system abnormality in Parkinson's disease. The results may also increase our understanding of visual hallucinations in other disorders. Conceivably, such knowledge could lead to strategies to prevent, minimize or treat such symptoms.-

Principal Investigator: JAHANSHAHI, MARJAN
Grant Number: 5R01NS040865-04
Title: DEEP BRAIN STIMULATION--COGNITION/MOTIVATION/MOOD IN PD

Abstract: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been shown to be an effective treatment for the motor symptoms of Parkinson's disease (PD), particularly improving akinesia and rigidity and reducing levodopa-induced dyskinesias. Neuropsychological investigations have shown that such beneficial effects of DBS on motor function are accompanied by significantly worse performance on specific tests of cognitive executive function such as word fluency and conditional associative learning, respectively when assessed after relative to before surgery or with stimulation on vs off. Surgery for DBS has also been reported to be associated with improvements of depression and anxiety, possibly as a result of the improved motor function, but also some loss of initiative and fatigue suggestive of apathy, a motivational deficit. DBS of the STN is based on current models of fronto-striatal functioning in normals and in PD. The proposed project will involve a more detailed investigation of the impact of DBS on specific tests of executive function (word fluency, random number generation) and learning (conditional associative learning, motor sequence learning) and on mood and motivation using a series of clinical neuropsychological and PET activation studies. The specific aims are: 1.To conduct a number of clinical neuropsychological studies to compare the effects of stimulation on vs off and determine whether DBS results in significant deterioration on tests of cognitive executive function such as word fluency and on tests of learning such as conditional associative learning and motor sequence learning and to clarify the precise nature of the deficits on these tests with stimulation. The impact of DBS on mood and motivation will also be assessed before and 3 months after surgery using a series of standardized questionnaires and interview schedules and the association of these changes to changes in disability and quality of life will also be investigated. 2.To use PET activation studies to identify the mechanisms of change in executive function and learning with DBS of the STN in PD. The effect of stimulation on vs off on regional cerebral blood flow will be measured while patients perform tests of executive function (phonemic word fluency or random number generation), learning (conditional associative learning or motor sequence learning) or matched control tasks and during a choice RT with or without manipulation of motivation (provision of feedback and incentive for fast responses). Any changes in frontal and striatal activation and in fronto-striatal connectivity within and between the motor, associative and limbic circuits will be measured using techniques such as structural equation modeling and regression methods to

Principal Investigator: KOTZBAUER, PAUL T
Grant Number: 1K08NS048924-01
Title: Neurodegenerative consequences of PanK2 mutations

Abstract: The candidate is an M.D./Ph.D neurologist who is currently a trainee in the Center for Neurodegenerative Disease Research. His goal is to develop additional research skills and experience needed to become an independent clinician scientist working to understand the pathogenesis of neurodegenerative diseases. The proposed research project focuses on neurodegeneration with brain iron accumulation (NBIA), which causes progressive impairment of speech, movement and cognition. At the neuropathological level, NBIA is characterized by iron accumulation, inclusion formation, signs of oxidative stress, and death of multiple neuronal populations. These features are also seen to varying degrees in other neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease. Mutations in the gene for pantothenate kinase 2 (PanK2) were recently identified in a subset of NBIA cases. The PanK2 gene encodes an enzyme involved in coenzyme A (CoA) synthesis, a critical pathway linked to a number of cellular processes, including fatty acid synthesis, energy production, and possibly, synthesis of anti-oxidant molecules. The long term objectives of this project are to understand how PanK2 mutations lead to iron accumulation, oxidative stress, inclusion formation, and neuronal death. The proteolytic processing, mitochondrial localization and in vitro catalytic properties will by characterized for mutant Pank2 proteins and compared to the wild type human PanK2 protein. Cell culture systems will be established in which PanK2 expression is eliminated and in which wild type or mutant PanK2 proteins are over-expressed. Mice that lack PanK2 expression will also be generated. Cell lines and mice lacking PanK2 expression will be examined for changes in levels of biochemical intermediates hypothesized to be dependent on PanK2 function. Finally, neuronal and non-neuronal cells lacking PanK2 will be examined for signs of increased oxidative stress, susceptibility to oxidative injury, cellular and mitochondrial import of radio labeled iron, and inclusion formation.-

Principal Investigator: LAURIENTI, PAUL J
Grant Number: 5K08NS042568-02
Title: The Effect of Aging on Cross-Modal Sensory Processing

Abstract: The research project is designed to study cross-modal sensory processing in aging as it has been shown that all sensory systems exhibit diminished function with age and recent studies have suggested that the integration of information from multiple sensory modalities (cross-modal processing) is affected by normal aging, interestingly, many of the disabilities associated with aging that impact the quantity of life, such as increased fates, communication disturbances, and memory impairment may be associated with alterations of cross-modal processing. The Specific Aims for this project are purposely designed to identify behavioral and neural changes in cross-modal processing that occur with age. Neural responses will be measured using functional magnetic resonance imaging (fMRI). Subjects will be studied during passive cross-modal stimulation, during a cross-modal matching task, and during a cross-modal integration task. Neural activation patterns and behavioral data will be analyzed to identify dysfunctional brain areas that correlate with diminished cross-modal processes. Because cross-modal processes are intimately involved in nearly all aspects of sensory processing and play critical roles in language processing, spatial orientation, and memory, a better understanding of changes that occur with age may help shed light on many of the problems experienced by aged individuals. The candidate has completed clinical (M.D,) and basic science (Ph.D.) training and has the desire to pursue a career in clinical research. The training program will include didactic instruction in statistics and statistical software programming. Through the guidance of his co-mentors, the candidate will master the skills necessary to perform scientific studies in patient populations. His goal is to combine the information acquired throughout his education to enable him to study diseases of the human brain as an independent investigator. The Wake Forest University School of Medicine is an environment that will allow the applicant to excel in the clinical neurosciences. The Department of Radiology has an active fMRl research program and is dedicated to expanding the neuroimaging research group. The J. Paul Sticht Center on Aging and Rehabilitation serves as the hub of research and teaching activities as well as a key location in the clinical treatment of elderly patients.-

Principal Investigator: LEONARD,
Grant Number: 5R01NS027881-10
Title: Synaptic Modulation of Mesopontine Cholinergic Neurons

Abstract: Chronic or intermittent sleep disorders such as narcolepsy, sleep apnea, and insomnia afflict nearly 40 million people in the United States. Yet the neural mechanisms controlling both normal sleep and its pathologies remain poorly understood. Considerable evidence indicates that mesopontine cholinergic neurons are critical for this control and that their disregulation is involved in narcolepsy, Parkinson's disease, supranuclear palsy and depression. The long-term goal of this project is to understand the synaptic and non-synaptic mechanisms regulating activity of mesopontine cholinergic neurons. Recent compelling evidence indicates that disruption of the novel Hypocretin/Orexin (Hcrt/Orx) peptide system results in narcolepsy - a sleep disorder characterized by excessive daytime sleepiness, sleep fragmentation and the intrusion of rapid eye movement sleep behaviors into wakefulness. Anatomical evidence and our data indicate that mesopontine cholinergic neurons are important targets of these peptides. This proposal focuses on identifying the mechanisms by which Hcrt/Orx acts upon mesopontine cholinergic neurons and associated sleep-related neurons. We will investigate the general hypothesis that Hcrt/Orx peptides regulate both the short-term and long-term excitability of sleep-related neurons. To do so we will use whole-cell recording and calcium imaging methods in brain slices obtained from control mice and mice lacking the two known orexin receptors. We will address this hypothesis by 1) characterizing the ionic currents responsible for the post-synaptic excitatory actions of Hcrt/Orx peptides; 2) Identifying the sources and consequences of intracellular [Ca2+] changes produced by Hcrt/Orx peptides; 3) Identifying the specific roles of each orexin receptor by utilizing single and double receptor knockout mice and 4) Investigating possible alterations in neuron excitability in the mouse double orexin receptor knockout model of narcolepsy. Collectively, these results will advance the understanding of the molecular and cellular mechanisms underlying sleep regulation and its pathology. -

Principal Investigator: MARDER, KAREN S
Grant Number: 2R01NS036630-05A1
Title: Genetic Epidemiology of Parkinson's Disease

Abstract: In the first funding period, we compared the risk of PD in relatives of 221 PD patients with age at onset (AAO) < 50 to relatives of 266 PD patients with AAO >50 and 409 controls. The magnitude of increased risk of relatives of PD cases vs. controls was similar in early-onset cases (RR: 2.9, 95%C1: 1.6-5.0) and late onset cases (RR: 2.7, 95%CI: 1.6-4.4). However in families of early-onset cases, the degree of increased risk was much greater in siblings (RR: 7.9, 95%C1: 2.5-25.5) than in parents (RR: 1.7, 95% CI: 0.9-3.3), consistent with an autosomal recessive contribution to inheritance. In late-onset families, risk was elevated in both parents and siblings, inconsistent with a recessive model. Mutations in the parkin gene have emerged as the most important causative or risk-raising factor in early-onset PD. In this second competitive renewal application, we have redesigned our study to make optimal use of 300 early onset cases already recruited at the Columbia site (200 not yet screened for parkin mutations) and the 40 PD cases with parkin mutations we have already identified. We will join with investigators at 7 other sites who will contribute an additional 600 cases with age of onset < 50 and 21 identified parkin families to form a US Parkin Consortium. Our first aim is the expansion of 125 PD cases that carry parkin mutations to include 1st and 2nd degree relatives. We will determine whether the risk of psychiatric and cognitive manifestations in asymptomatic gene carriers who do not meet criteria for PD is higher than in asymptomatic non-gene carriers. Identification of a parkin carrier phenotype will provide clues to etiopathogenesis and may define the appropriate time for early therapeutic intervention. Our second aim is to define the distribution of age specific penetrance in 100 of the 125 families who were recruited solely be age of onset, so as not to bias these estimates upward by inclusion of "high risk" families recruited because they are multiplex. We will compare differences in age specific penetrance by allelotype (heterozygous vs. homozygous or compound heterozygous). The results of this study will clarify the role of parkin in genetic susceptibility and foster the development of genetic testing guidelines. The consistent finding that at least 30 percent of PD patients with parkin mutations are heterozygotes, despite that fact that inheritance was initially described as recessive, and new availability of commercial testing make this study both critical and timely. -

Principal Investigator: MENZA, MATTHEW A
Grant Number: 5R01NS043144-02
Title: Treatment of Depression in Parkinson's Disease

Abstract: Depression is the most common neuro-psychiatric disorder found in patients with Parkinson's Disease (PD). It causes immense personal suffering, and is associated with increased disability and caregiver burden. Despite the adverse consequences of depression in patients with PD, there are virtually no empirical data to guide clinical treatment. In the absence of data, the SSRIs are apparently used as the first-line treatment, despite concerns about efficacy, safety, and tolerability in this population. This proposal is for a pilot study to establish the feasibility of, and generate sufficient data to plan, a larger clinical trial that will be able to inform clinical treatment of these patients. This pilot trial will (AIM 1) examine the feasibility of a larger trial, and establish (AIM 2) the effect size for short-term efficacy of anti-depressants, compared to placebo, in this population. It will also (AIM 3) evaluate the effect of long-term depression treatment on quality-of-life. This will be done in the context of a placebo-controlled, double-blind, parallel group, flexible dose trial of an SSRI (Paroxetine), a tri-cyclic (Nortriptyline) and placebo in acute (8 weeks) and long-term treatment (6 months). A total of 75 patients with PD (without significant motor fluctuations or Dementia) and depression (major depression or Dysthymia) will be randomized to each of the three arms in a balanced design. The feasibility issues that will be explored include recruitment, retention, drug tolerability, and the ability to maintain the blind. The outcomes that will be explored for the acute phase include changes in the Hamilton Depression Rating Scale (HAM-D) score, and the percent of patients who are responders (>50% improvement in the HAM-D, or < 10 on the HAM-D). The outcome variables explored for the long-term phase include the Parkinson's Disease Questionnaire and the Medical Outcome Study Short Form. Secondary analyses will involve the exploration of anxiety, motor disability, sleep, cognition, and individual or clusters of symptoms that are responsive to treatment in order to facilitate planning a subsequent, full-scale clinical trial. -

Principal Investigator: MOSLEY, RODNEY L
Grant Number: 1R21NS049264-01
Title: Neuroprotective Vaccination for Parkinson's Disease

Abstract: Microglia inflammation contributes, in significant measure, to the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) during idiopathic Parkinson's disease (PD). Attenuation of such inflammation could attenuate disease. To this end we show that microglial deactivation responses, induced by vaccination, in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) intoxicated mice improves dopaminergic neuronal survival. This was achieved by adoptively transferring spleen cells from copolymer-1 (Cop-1) immunized mice to MPTP-treated recipients. Spleen cells from ovalbumin (OVA) injected mice failed to affect neuronal protection. Thus, our preliminary works show that protection from dopaminergic neurodegeneration can be achieved by adaptive immunity with T cells specific for Cop-1. Based on response kinetics, antigen specificity, and functional adaptive T cell immune responses, we predict that the mechanism(s) of neuroprotective immunity can be realized and could provide novel treatment strategies for human disease. Our hypothesis posits that protection from dopaminergic neurodegeneration by Cop-1 vaccination is generated through immune cell-mediated mechanisms with specificity for Cop-1 peptides and self-antigens. To investigate this we will adoptively transfer T lymphocytes, B cells and monocytes from Cop-1 immunized mice into MPTP-treated animals. Neuroprotection will be assessed by numbers of dopaminergic neurons, neurotransmitter levels, and neuronal metabolites by magnetic resonance spectroscopic imaging (MRSI). Immune cell populations, proven relevant to neuroprotection will be evaluated for the expression of gene products that are cell population specific as candidates for neuroprotection. Genetic fingerprint analysis will include cDNA microarray analysis and proteomics. This approach takes advantage of an integrated and well-established research program within the Center for Neurovirology and Neurodegenerative Disorders and builds upon research activities in PD supported previously through private donations. These approaches could prove useful for treatment of human PD. -

Principal Investigator: OKUN, MICHAEL S
Grant Number: 5K23NS044997-02
Title: DBS Effects on Mood and Cognition in Parkinsons Disease

Abstract: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus interna (GPi) has been demonstrated to be effective in the treatment of the cardinal motor symptoms of Parkinson's disease (PD) (tremor, rigidity, and bradykinesia). Both STN and GPi DBS have been documented to be effective in treating parkinsonian motor signs. Due to early limited reports, which suggest more robust improvements in UPDRS motor scores, and the ability to reduce parkinsonian medication with STN, but not GPi, STN has been the preferred target of most centers. There is, however, increasing evidence that STN DBS may be associated with a significant number of mood and cognitive changes. Because of the small size of the STN (158mm3), stimulation within the sensori-motor area can result in spread to limbic and associative areas of STN as well as to surrounding structures and fiber systems that may also affect mood and cognition. Since the Gpi (478mm3) is significantly larger than STN, a lead can be placed in the sensorimotor territory of the GPi with less likelihood of current spread to non-motor portions of the GPi or to adjacent structures and fiber systems that can adversely change mood and cognition. In this proposal we will 1) Characterize and compare the mood and cognitive changes associated with STN and GPi DBS, 2) delineate regions within or around the STN and GPi that are associated with specific mood and cognitive changes during DBS in these regions, and 3) assess the relative effect of right versus left STN or GPi stimulation on mood and cognition. This study will characterize the types and incidence of mood and cognitive changes that occur during stimulation in STN and GPi. It will also compare the relative changes in mood and cognition that occur in each site and examine the role of lead location in mediating them. The research is part of a five-year plan for training and career development for the Principal Investigator. This proposal includes active and experienced mentoring, access to diverse resources, and a scientific environment suited specifically for the development of the PI as an independent physician scientist.-

Principal Investigator: RAGOZZINO, MICHAEL E
Grant Number: 5R01NS043283-02
Title: Striatal Acetylcholine and Behavioral Flexibility

Abstract: The main objective of this proposal is to build a greater understanding of how the striatal cholinergic system contributes to behavioral flexibility. There is accumulating evidence that neurological and psychiatric disorders that lead to striatal neuropathology, i.e. Parkinson's disease, Huntington's disease and schizophrenia, produce severe deficits in cognitive flexibility. In addition to the common cognitive symptomology, Parkinson's and Huntington's disease patients both exhibit decreases in cholinergic markers in the anterior regions of the caudate and putamen. At present, unknown is what striatal circuitry or neurochemical mechanisms underlie cognitive flexibility. Advances in elucidating the etiology of these disorders and development of effective treatments for the cognitive deficits relies, in part, on identifying the basic neurochemical mechanisms within the striatum that underlie the cognitive functions impaired in Parkinson's and Huntington's disease. The first goal of the proposal is to understand the dynamic changes in acetylcholine output in the dorsomedial and dorsolateral striatum during acquisition and reversal learning of a visual cue discrimination, using in vivo microdialysis with high pressure liquid chromatography. Recent timings in Parkinson's disease patients suggest that anti-cholinergic treatments lead to cognitive flexibility deficits. The second goal of the proposal is to determine whether specific muscarinic receptor subtypes in the dorsomedial striatum contribute to behavioral flexibility. Previous studies found that dopamine activity in the striatum also influences cognitive flexibility. Furthermore, extant research indicates an interaction between the dopaminergic and cholinergic systems in the basal ganglia related to motor behavior. The third goal of the proposal is to determine whether dopamine D1 and/or D2 receptors modulate acetylcholine efflux in the dorsomedial striatum to influence behavioral flexibility. Overall, this approach takes a unique approach in examining the dynamic changes in striatal acetylcholine release during the actual learning and shifting of strategies. The proposed studies will also provide complimentary information on the specific muscarinic receptors that may facilitate behavioral flexibility in the dorsomedial striatum. Moreover, the proposed studies can help unravel the complex interaction of neurotransmitters in specific striatal circuitry as it relates to behavioral flexibility. The findings from these experiments may enable the development of selective and targeted pharmacological interventions to alleviate the cognitive symptomology in Parkinson's and Huntington's disease without producing unwanted motoric side effects. -

Principal Investigator: RICHARD, IRENE H
Grant Number: 1R01NS046487-01A1
Title: Study of Antidepressants in Parkinson's Disease (SAD PD)

Abstract: Depression is common in patients with Parkinson's Disease (PD), and is a major factor negatively impacting quality-of-life. To date, there have been no well-designed clinical trials of anti-depressant pharmacotherapy for depression in PD. Selective Serotonin Reuptake Inhibitor (SSRI) and, more recently, combined Serotonin and Norepinephrine Reuptake Inhibitor (SNRI) anti-depressants are used as a first-line treatment for depression. However, their efficacy and tolerability in PD have not been established, and there are several important reasons why results from studies in primary psychiatric populations cannot simply be extrapolated to patients with PD. In PD, the underlying pathophysiology and somewhat atypical depressive features may result in a different anti-depressant response. Furthermore, PD patients are particularly vulnerable to antidepressant-induced extrapyramidal side effects, and a host of factors (including concomitant anti-Parkinsonian medications) may affect the general tolerability of these agents. The proposed clinical trial has been designed to compare the efficacy and tolerability of Paroxetine (an SSRI) and Venlafaxine (an SNRI) in PD patients with depression. Information regarding the effects of these medications on motor function, quality-of-life, and cognition will also be obtained. Two-hundred, twenty-eight subjects will be enrolled among 15 centers, and each subject will participate in the trial for 12 weeks. The trial will clarify many important questions regarding the treatment of depression in patients with PD. -

Principal Investigator: RICHARD, IRENE H
Grant Number: 5K23NS002184-05
Title: MOOD FLUCTUATIONS IN PARKINSON'S DISEASE

Abstract: The candidate has a clinical background in neurology with an expertise in movement disorders and has completed a two year NIH-funded fellowship through the Department of Neurology in Experimental Therapeutics. This fellowship provided the candidate with both theoretical knowledge and practical experience pertaining to the design and conduct of clinical trials. She has focussed most of her efforts thus far on the understanding and treatment of the behavioral aspects of Parkinson's disease (PD) The candidate's short term goals include the following: 1) to increase her knowledge of basic pharmacology and gain experience using techniques relevant to pharmacologic mechanism oriented research, 2) to gain a better understanding of molecular medicine, 3) to obtain training in psychiatric assessment techniques, 4) to expand her knowledge of areas fundamental to clinical investigation including biostatistics, epidemiology and outcomes research. The focus of her research plan during this career development award will be understanding mood fluctuations in PD. Mood fluctuations have been reported in up to 2/3 of advanced PD patients who experience motor fluctuations. These can be frequent, dramatic and distressing. Research involving the phenomenology and underlying mechanisms of mood fluctuations in PD has been limited. The specific aims of this study are to: 1) better understand the phenomenology of mood fluctuations in PD (frequency, quality, magnitude), 2) better understand the relationship between mood fluctuations and more pervasive depressive disorders in PD, 3) clarify the temporal relationship between changes in mood and motor states in PD, 4) elucidate the neurobiological mechanisms of changing mood states in PD and to determine, in particular, whether mood fluctuations in PD are the result of dopamine dysregulation, and 5) gather preliminary information regarding the optimal treatment of mood disorders in PD. These findings may lead to the development of therapeutic interventions for patients with PD who suffer from these disabling fluctuations on a daily basis. It may also provide a better understanding of the mechanisms responsible for more pervasive forms of depression in PD, and perhaps even in primary psychiatric mood disturbances. -

Principal Investigator: RODRIGUEZ, ALICE L
Grant Number: 1F32NS049865-01
Title: Development of allosteric potentiators of mGluR4

Abstract: Treatment of Parkinson's disease (PD) has traditionally focused on dopamine replacement strategies such as LDOPA. While generally effective early on, L-DOPA has often proven inadequate for long term treatment due to serious adverse side effects. Recent studies in Dr. Conn's laboratory suggest that activators of metabotropic glutamate receptor mGluR4 may provide a novel pharmacological approach to the treatment of PD by targeting the indirect pathway of the basal ganglia. Furthermore, Dr. Conn and coworkers have developed a novel approach to activation of mGluR4 by development of allosteric potentiators that do not activate this receptor directly but dramatically potentiate the response to glutamate. While these studies provide an exciting proof of principle for a novel approach to activation of mGluR4, there is a need to develop novel compounds that have a higher potency and are useful for further in vivo studies. The goal of this work is to develop novel potent and selective allosteric potentiators of mGluR4. A threefold approach will be implemented, beginning with performing a high throughput screen mining for compounds that potentiate the glutamate response of mGluR4. In parallel with the HTS, medicinal chemistry studies will be pursued to improve upon the properties of known potentiators. Finally, mutagenesis studies will be performed to develop a better understanding of the molecular interactions involved in potentiator binding which will subsequently aid in the design of future compounds. Together these approaches will result in the development of novel small molecules that have a therapeutic effect on PD by reducing transmission through the indirect pathway. Furthermore, these studies will be complemented by ongoing electrophysiology and behavioral studies in Dr. Conn's laboratory that will determine the effects of these compounds in vitro models of basal ganglia function. -

Principal Investigator: RUOHO, ARNOLD E
Grant Number: 5R01NS033650-09
Title: Characterization of Vesicular Monoamine Transporters

Abstract: The strategy of this proposal is based on the rationale that identification of the inhibitor, substrate, proton translocation, and functionally relevant phosphorylation sites on monoamine transporters (VMAT2) will provide a basic understanding of the mechanism of action of monoamine sequestration into vesicles and the factors which regulate transporter activity. This work will be accomplished in three Specific Aims: (1) Identification of the reserpine binding site(s) on VMAT2. Novel reserpine photoaffinity labels will be synthesized and characterized, and photo-labelled peptides will be identified in order to map the reserpine binding site; (2) Identification of the substrate transport channel. This aim will involve the use of several approaches, including radioactive photo-activatable substrate analogs to covalently derivatize the substrate binding site on VMAT2; site-specific derivatization of VMAT2 at engineered cysteine residues with the cysteine-reactive reagents, methanethiosulfonate ethyl amine (MTSEA), and MTS-ethyltrimethylammonium (MTSET); and site-directed mutagenesis of potential residues lining the channel; (3) Determination of the functional role of two highly charged regions of VMAT2. This aim will involve the use of biochemical and genetic (site-directed mutagenesis) approaches to determine the role of phosphorylation of the N-terminus of VMAT2 on transporter function and the intracellular distribution/oligomeric state of the transporter. Reduced or aberrant activity of the monoamine transporter of the synaptic vesicles in dopaminergic neurons of the substantia nigra through either direct or indirect actions of toxicants (e.g., MPP+, insecticides) and genetically altered neuronally expressed proteins may play a central role in Parkinson's Disease. The regulation of uptake of monoamine neurotransmitters into storage vesicles may also play an important role in affective psychological disorders related to depression by altering levels of serotonin, norepinephrine, dopamine, or other neurotransmitters. This work will provide insight into the mechanism of action of the monoamine transporters and contribute to our understanding of how pharmacological and therapeutic strategies may be devised to treat Parkinsonism or other disorders of the nervous system. -

Principal Investigator: RYE, DAVID B
Grant Number: 5R01NS043374-03
Title: Circuitry of Midbrain Dopamine in Sleep & Wake

Abstract: Dopamine (DA) is a neurotransmitter that modulates diverse waking behaviors including movement, motivation, cognition, reward, and feeding. Less appreciated and understood are dopamine's influences upon normal and pathologic sleep. Dopamine cell death which occurs in Parkinson's disease, is associated with profound alterations in wake-sleep state that can be broadly classified into disturbances of noctural movement and thalamocortical rhythmicity. The former include periodic leg movements of sleep and rapid-eye-movement sleep (REM-sleep) behavior disorder, while the later encompass loss of sleep spindles and slow-wave sleep, daytime sleepiness, and daytime intrusion of REM-sleep manifesting as hallucinatory behavior. Heuristic models of disease have limited themselves largely to DA's indirect, rather than direct actions upon thalamocortical circuits, and also to DA's participation in waking behaviors rather than thalamocortical arousal state (e.g., sleep). We have recently described a novel mesothalamic dopamine pathway originating via axon collaterals of the nigrostriatal pathway and which degenerates in PD. Mesencephalic dopamine neurons therefore have potential to modulate normal and pathologic behavior, including sleep, not only through traditional nigrostriatal pathways, but also by way of axon collaterals to the thalamus. Here we propose to define anatomical and physiological features of these novel circuits in non-human primates. S.A. number 1 employs microscopic techniques to establish the distribution, subcellular targets, topography, and collateralization of DA innervation in "motor", "prefrontal", "limbic" and the reticular (i.e., the thalamic pacemaker) thalamic nuclei. S.A. number 2 will extend our preliminary electrophysiological demonstration of DA modulation of thalamic neural activity, by characterizing the responsivity of the same nuclei to focal dopaminomimetics. S.A.number 3 examines the state-related firing of midbrain DA neurons identified on the basis of their thalamic targets, and the state-related release of DA from functionally homologous striatal regions. These studies are a prerequisite to advancing our understanding of the pathophysiology and treatment of arousal disorders that accompany an array of neuropsychiatric conditions, particularly those which can be broadly defined as hyper- (e.g., schizophrenia) and hypodopaminergic (e.g., PD and restless legs/periodic leg movements of sleep).-

Principal Investigator: SABBAN, ESTHER L
Grant Number: 5R01NS028869-12
Title: Molecular Biology of Norepinephrine Biosynthesis

Abstract: Norepinephrine (NE) is a crucial catecholamine neurotransmitter/hormone mediating a wide range of physiological responses. Alterations in NE neurotransmission are associated with several prevalent disorders, including cardiovascular disorders such as hypertension/hypotension, neuropsychiatric disorders, such as depression and in Parkinson's disease. Regulation of the expression of NE-biosynthetic enzymes, tyrosine hydroxylase (TH) and dopamine beta-hydroxylase (DBH), is a key mechanism of regulation of the NE systems. The specific aims of this proposal are: 1.) Determine the kinetics and the persistence of activation of TH and DBH transcription in rat locus coeruleus with different duration or repetitions of immobilization stress. 2.) Examine the dynamics of pathways involved in transcriptional activation of TH and DBH gene expression in locus coeruleus and adrenal medulla with different durations or repetitions of stress. 3.) Identify the induction of de novo synthesis of transient or long-lasting transcription factors in rat adrenal medulla and locus coeruleus associated with regulation of TH and DBH gene expression by exposure to single and repeated immobilization stress. 4.) Begin to characterize the mechanisms by which the above observed stress responsive factors cross-talk to regulate TH and DBH gene expression. Specifically examine the interaction of AP-l factors and Egr1 on the regulation of TH transcription. The results will provide a crucial understanding of the different transcriptional mechanisms of activation of gene expression of catecholamine producing systems in the CNS and the periphery with acute and repeated exposure to stressful situations. These findings will contribute to the development of new strategies to prevent the harmful maladaptive changes in catecholamine neurotransmission, while enhancing its beneficial adaptive aspects -

Principal Investigator: SCHOR, NINA F
Grant Number: 5R01NS041297-03
Title: Antioxidant Strategies for Parkinson's Disease

Abstract: Reactive oxygen species (ROS) have been implicated in the pathogenesis of Parkinson's disease. This suggests that antioxidant strategies may be useful in the treatment and/or prevention of this neurodegenerative disorder. We have developed and implemented two models for the central movement disorder and autonomic peripheral neuropathy, respectively, associated with Parkinson's disease. We propose to use these models to design and test antioxidant strategies we have previously developed for adjunctive use with ROS-generating chemotherapeutic agents. We will further use our studies of the biochemical effects of antioxidant treatment to develop a screening test for new antioxidant agents for use in Parkinson's disease and other ROS-related disorders. Specifically, we propose to test the hypothesis that recycling antioxidants increase expression of p21 wafl/cip1,enhance binding of HIF-1 and CREB to DNA, activate NF-kappaB, prevent ROS-induced morphological apoptosis, and decrease ROS-induced membrane phospholipid and protein nitration in culture models of Parkinson's disease. We will further test recycling antioxidants for their distribution to the CNS and peripheral compartments, and use this information to test CNS-penetrating and non-CNS-penetrating agents for efficacy in the central and autonomic nervous system models, respectively, of Parkinson's disease. Finally, we will test the hypothesis that the magnitude of induced in vitro biochemical change for each drug correlates with the degree of protection from the effects of ROS in the CNS or autonomic model. This latter study will pave the way for development of an in vitro screening test for new antioxidant strategies proposed for use in Parkinson's disease. This application specifically addresses the NINDS agenda for research in Parkinson's disease in its development of in vitro screening tests for putative therapeutic agents in general and antioxidants in particular for this disease, its development of animal models for the clinical aspects of Parkinson's disease, and its potential for further elucidation of the mechanisms of ROS-induced apoptosis in the nervous system.-

Principal Investigator: TICKLE-DEGNEN, LINDA
Grant Number: 5R01NS048059-02
Title: Culture, Gender, and Health Care Stigma in Parkinsonism

Abstract: The overall goal of the proposed research is to understand the stigmatizing role of the movement disorder of Parkinson's disease (PD) in health care practitioners' assessment of patient psychological traits, in the patient-practitioner relationship, and in the development of intervention recommendations. The first specific aim of the research is to elucidate the consequences of the operation of movement stereotypes on practitioner impressions of and conclusions about patients with PD. The second specific aim is to document the interaction of expressive masking (the diminishment of normal movement) with gender and culture on stigma outcomes. The third specific aim is to determine the degree to which practitioner expertise moderates the stigmatizing role of expressive masking on practitioner perceptions of and conclusions about patients. The fourth specific aim is to evaluate the clinical utility of the findings from the perspective of expert practitioners. Twelve Taiwanese patients (6 females and 6 males) and 12 American patients (6 females and 6 males) will be videotaped during a standardized health care interview in their respective homelands. Within each group of 6 patients (gender crossed with culture), there will be 3 patients with high expressive masking and 3 patients with normal expressive movement. Excerpts from the resulting 24 tapes will be shown to expert and novice health care practitioners in Taiwan and the U.S. who will assess patients' social and mental competence and potential for entering into a successful therapeutic relationship. In addition, the practitioners will make quality-of-life intervention recommendations. The results of the study will be presented to expert practitioners, in focus groups, who will evaluate the clinical utility of the findings and make recommendations for interventions to reduce practitioners' stigma responses. It is anticipated that PD with expressive masking will be more stigmatizing than PD without masking, especially as demonstrated in outcomes for novice compared to expert practitioners. It is also anticipated that negative outcomes of masking will be greater for female than male and American than Taiwanese patients because of different norms associated with movement expression in these groups.-

Principal Investigator: York, Michele
Grant Number: 5K23NS041254-03
Title: Cognitive functioning following deep brain stimulation

Abstract: Dr. Michele York, under the mentorship of Dr. Harvey Levin, Director of Research of Baylor College of Medicine's (BCM) Physical Medicine and Rehabilitation Department and Professor of Psychiatry and Neurosurgery, and Dr. Robert Grossman, the Chairman of BCM's Neurosurgery Department, will more effectively evaluate the long-term cognitive effects of deep brain stimulation (DBS) for the treatment of Parkinson's disease (PD). The scientific objective of the proposed research plan is to more clearly understand the relationship between the frontostriatal neural circuitry affected by DBS and PD and cognitive functioning. The clinical objectives of the proposed research plan include improving upon the evaluation of outcome by improving cognitive diagnostic techniques, clarifying the clinical criteria for surgical selection, and incorporating analysis of post-operative magnetic resonance imaging (MRI) findings. To achieve these aims, Dr. York will compare the executive functioning of patients undergoing staged bilateral subthalamic (STN) and globus pallidus (GPI) DEIS to patients who receive the best medical management for the treatment of PD on verbal fluency measures administered under conditions of set shifting and attentional control and working memory measures, which are cognitive processes dependent on the functional integrity of frontostriatal circuitry. The relationship between DBS electrode placement and performance on these frontostriatal neuropsychological tasks will also be investigated. The objectives of the training program are to acquire practical and technical skills that will aid Dr. York in developing her career, specifically in the areas of neurosurgical interventions and neurological evaluations of PD, structural and functional neuroimaging, and the neuroscience of PD. This training will provide Dr. York with a better understanding of the cognitive deficits in PD and the mechanisms and consequences of emerging interventions for the treatment of this neurological disease. The training activities during the award period will consist of 3 major components: 1) Didactics through coursework, technical training seminars, rounds, and observation, 2) Supervisory Guidance through regularly scheduled meetings with mentors and an Advisory Committee, and 3) Instruction in the Responsible Conduct of Research. Dr. York will gain the necessary knowledge to attain her long-term career goal of working as an independent clinical researcher by acquiring the background and skills in neuroscience, neuroimaging, and grant preparation needed to write a ROI proposal to adapt these cognitive tasks to a functional imaging setting to further elucidate the neural mechanisms of PD and DBS. -